REMARKS

The pending claims require a fusion protein comprising a combination of two specific elements, namely (i) tetanus toxin fragment C and (ii) a polypeptide comprising at least 6 contiguous amino acids of sequence of pre-S1 of hepatitis B virus (HBV). The claims also require that the combination induces antibody that recognises pre-S1 of HBV. A concept underlying the invention is that the fragment C presents the pre-S1 sequence to the immune system in such a way as to enhance the antibody response against the pre-S1 sequence.

The experimental data in the application show that the combination induces a good antibody response against pre-S1. See, for example, Figure 3B of the application. The anti-pre-S1 titer is of the same order of magnitude as that against the fragment C component of the combination. See Figure 2B.

Contrary to the Examiner's argument, for reasons explained below Applicant's belief is that it was not obvious to combine the cited references, Khan et al., Shi et al. and Mimms et al., and thereby devise the combination of elements required by the claims. Furthermore, the antibody response against pre-S1 induced by the combination is far higher than would have been expected from the cited references.

The test for obviousness over a combination of references involves a consideration of whether it was obvious to make that combination in the first place. For example, as explained in the USPTO Manual of Patent Examining Procedure:

> "[*T*]*here must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. The Federal Circuit has produced a number of decisions overturning obviousness suggestions due to a lack of suggestion in the prior art of the desirability of combining references. . . .*" (MPEP § 2145, X.C.)

Applicant respectfully submits that the Examiner has not put forward any convincing reason why a skilled person would have combined the cited references. In particular, the Examiner has not put forward any convincing reason why a skilled person would have focussed simultaneously and specifically on the disclosure relating to fragment C in Khan et al. and on the disclosure relating to pre-S1 in Mimms et al. The Examiner seeks to justify the combination of references as follows:

> "*Appellants' argument has been considered; however, it is not persuasive because art teaches that HBV surface antigen peptide vaccine needs to be modified for enhancing its immunogenicity and expression as evidenced by Shi et al.*" (Page 5, first full paragraph, of Examiner's Answer.)

The Examiner's argument is unfounded. In order for it to have been obvious to combine the references as the Examiner suggests, there must have been some motivation for a skilled person not merely to modify HBV surface antigen peptide but to modify it specifically by combining it with fragment C of tetanus toxin; there must have been an obvious reason why a skilled person would have chosen this modification out of all the other possible modifications which could have been made. However, such an obvious reason does not in fact exist. For that reason alone, the Board should reverse the Examiner's finding of obviousness.

Applicant asked an expert in immunity against hepatitis B, Dr. Mark Page, to review the rejection. Dr. Page's comments are set forth in a Declaration from him of record dated April 9, 2002. As Dr. Page explains in his Declaration, there were a very large number of carriers known in the art. For example, the following had been used as carriers:

keyhole limpet hemocyanin (KLH),
gelatin,
albumin,

ovalbumin,

casein,

bovine gammaglobulin (BGG),

erythtrocytes,

lipopolysaccharide (LPS),

caroboxymethyl cellulose,

poly-DL-lysine,

mycobacterial heat shock proteins,

micelles,

liposomes,

virosomes,

immune stimulating complexes (ISCOMs),

proteosomes,

β-galactosidase,

bacterial outer membrane and periplasmic proteins,

hepatitis B core antigen,

hepatitis B surface antigen,

retroviral Gag proteins,

phage coat proteins,

retrotransposon Ty protein p1,

the B subunit of heat labile toxin of *E.coli*, and

the B subunit of cholera toxin.

The number of known antigenic sequences that could potentially be linked to each of these carriers was even greater than the number of potential carriers. Khan et al., cited by

the Examiner, by itself lists a very large number of antigenic sequences in the passage bridging pages 5 and 6. It lists antigenic sequences of:

HIV such as HIV-1 and HIV-2, e.g., the CD4 receptor binding site from HIV;
hepatitis A virus;
hepatitis B virus;
human rhinovirus such as type 2 or type 14 rhinovirus;
herpes simplex virus;
poliovirus type 2 and 3;
foot-and-mouth disease virus (FMDV);
rabies virus;
rotavirus;
influenza virus;
coxsackie virus;
human papiloma virus (HPV), such as HPV type 16 and the E7 protein thereof and fragments of the E7 protein;
simian immunodeficiency virus (SIV);
Bordetella pertussis such as the P69 protein and filamentous heamagglutinnin (FHA);
Vibrio cholerae;
Bacillus anthracis;
E.coli such as the B subunit of heat labile toxin (LTB), the K88 antigens and enterotoxigenic antigens;
the cell surface antigen CD4;
Schistosoma manosi such as p28 glutathione S-transferase antigens (p28 antigens);
flukes;
mycloplasma;
roundworms;

tapeworms;

Chalmydia trachomatis; and

malaria parasites.

Thus, there were a vast number of combinations of carrier and antigenic sequence that could in theory have been dreamt up by a person skilled in the art. Out of all these possible combinations, there was no motivation in the art whatsoever to focus on both fragment C and pre-S1 and put the two together. This specific selection was not an obvious selection when viewed in the "real life" context of all the other combinations that a person skilled in the art might in theory have put together. Dr. Page puts it as follows in paragraph 6 of his Declaration:

> "*Thus, there were a vast number of combinations of carrier protein and antigenic sequence that could in theory have been put together by a scientist working in the field. I am not aware of any particular reason why a scientist would have chosen to put together fragment C and pre-S of hepatitis B out of all the other possible combinations that could potentially have been put tog[e]ther. The references cited by the Examiner, EP-A-389983 of Mimms, WO 94/03615 of Khan et al. and Shi et al., were not references which were high profile references in the field and I cannot see any particular reason why a scientist would have put the three of them together.*"

Applicant believes that the Examiner's reasoning is improperly tainted by hindsight. The Examiner's approach necessarily involves selecting a relatively small number of documents out of a vast state of the art, which documents were identified in a search specifically directed at the claimed invention. However, it must be borne in mind that a skilled person working before the priority date would not have carried out such a search in the absence of any motivation to do so. The Examiner has the benefit of hindsight knowledge of the claimed invention to provide motivation, but the skilled person working at the relevant time would not have had this benefit and would therefore not have put together the combination of documents cited by the Examiner.

In assessing obviousness, it is also necessary to bear in mind that the design of immunogens is an unpredictable art. Dr. Page puts it as follows in paragraph 7 of his Declaration:

> "*The design of immunogens is an empirical art. It is difficult or impossible to predict in advance whether a particular polypeptide will induce a good immune response such as an antibody response. In order to find out whether a polypeptide will induce such a response, it is necessary to make the polypeptide and test it in animal models. It is generally not possible to predict in advance with any reasonable degree of certainty whether a given polypeptide will work or not.*"

The Examiner did not find convincing Applicant's argument that the success of the claimed fusion proteins was not reasonably predictable. However, the unpredictability is in fact illustrated by comparing the results presented in Khan et al. with those presented in the instant application. The only results presented in Khan et al. showing antibody production induced by fragment C-based fusion proteins are for fusion proteins comprising fragment C fused to the P28 protein of *Schistosoma manosi* or to varying numbers of copies of a peptide corresponding to residues 115-131 thereof. (Example 6-9 on pages 28-31 of Khan et al. describe production of further fragment C-based fusion proteins, but no results are presented showing induction of antibodies.) Khan et al. found that (page 25, lines 13-14):

> "*No antibody responses to the monomeric fusion were detected.*"

In other words, Khan et al. found that "*no*" antibody responses were detected against a fusion protein comprising fragment C fused to one copy of the peptide corresponding to residues 115-131 of the P28 protein. Responses were only seen against fusion proteins comprising multiple copies of the peptide or the full length P28 protein.

In contrast, the results presented in the instant application show that even a single copy of a pre-S1 epitope is able to induce a potent antibody response. See, e.g., the table on page 18 and Figure 3B. These results would not have been predicted from Khan et al. because, as mentioned above, Khan et al. shows that a fusion protein comprising fragment C fused to one copy of a peptide immunogen does not induce an immune response against the immunogen.

The unpredictable nature of the results presented in the instant application is further illustrated by Shi et al. Shi et al. describes fusion of cholera toxin B subunit (CTB) to pre-S2 epitope. The fusion protein produced an extremely low antibody titer against the pre-S2 region. This is clear from, for example, Figure 7 on page 936 of Shi et al. The Figure shows that the peak antibody titer against CTB was about 5000, whereas the peak titer against pre-S2 was only about 140. A different scale had to be used for the anti-pre-S2 titer compared to that for the anti-CTB titer in order to present the anti-pre-S2 titer on the graph! The peak anti-pre-S2 titer was about 35 times less than the peak anti-CTB titer.

The Examiner rejects Applicant's argument that the low anti-pre-S2 titer shown in Shi et al. created low expectations. In doing so, the Examiner points to some speculation in Shi et al. as to why their titers were low. As noted by the Examiner, Shi et al. argues that the low titers may be explained either by a small amount of pre-S2 component in the fusion protein or by a poorly-sensitive assay for anti-pre-S2 antibody. See the first paragraph of the Discussion section of Shi et al. bridging pages 936 and 937. Shi et al. describes a potentially more sensitive assay in which the ELISA plate was coated with CTB-pre-S2 fusion protein instead of with HBsAg particles (Dane particles) and reports that the assay produced a higher titer of "preS2" (quotation marks in the original). However, as Shi et al. itself recognizes, the potentially more sensitive assay is not valid because it may not provide a true measure of the amount of relevant antibody.

It is clear from a reading of Shi et al. as a whole that its authors did not really know why they obtained a low antibody titer against pre-S2. The authors put forward two possible reasons for the low titre, but these are little more than speculation. As Dr. Page explains in paragraph 10 of his Declaration:

> "*The discussion section of Shi et al. on pages 936-937 puts forward various possible reasons for the extremely low titre of pre-S2 antibody but does not reach any firm conclusions. It was apparently not clear to the authors of Shi et al. why the titre was so low.*"

The fact that the authors of Shi et al. were not able to predict the reasons for the low titer with any degree of certainty illustrates the unpredictability in the art. Shi et al. did not allow prediction that the combination of fragment C and pre-S1 as recited in the claims would produce a good antibody titer against pre-S1. On the contrary, if anything Shi et al. created an expectation of low titers, particularly when combined with the showing in Khan et al. that a fragment C-peptide monomer fusion protein induced "no" antibody against the peptide.

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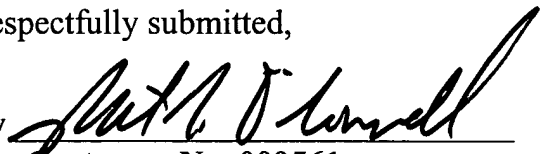
Respectfully submitted,

Dated: October 10, 2003

By 

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